REMARKS

1. By entering this Amendment, claims 1, 19-23, 25-26, 28-31, 33, 35-38, 40-41, 43-45, & 48 will be pending in the application, with claims 19, 25, 28, 35, and 40 withdrawn from consideration.

2. The Examiner requires the Applicants to update the status of all US applications cited. The Applicants respectfully point out that the amendment to the specification in the Applicants' previous Amendment & Response updated that status of all patent applications disclosed (e.g., page 4, lines 16-22, and on pages 13 to 14 of the instant application).

3. Regarding the Examiner's requirement to change the relationship of the application from a continuation to a continuation-in-part, the Applicants point out that the claims as amended herein are claims corresponding to the language in the specification as filed. Accordingly, this application is a continuation application of the prior filed application with no new matter. Specifically, claims 1, 26, 33, and 38 have been amended to recite the nature of the shed antigen (see p.14, lines 16-19; p. 5, lines 5-10; p. 13, lines 7-15); to recite the specific determinants recognized by the antibody; to recite the specific B cell subpopulations that are the target of the method and composition (see., e.g., p. 5, lines 10-13; p. 8, lines 10-15; Example 1, Table 2, and page 20, lines 6-20). Examples of shed antigen are taught in the specification (p. 14, lines 1-5) which therefore supports the claims (22, 23, 30, 31, 37, 38, 43, 44, 48).

> The amount of detail required to be included in claims depends on the particular invention and the prior art, and is not to be viewed in the abstract but in conjunction with whether the specification is in compliance with the first paragraph of section 112: "If the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Chemcast Corp. v. Arco Industries Corp.* 854 F.2d 1328 (Fed. Cir. 1988) citing *Georgia-Pacific Corp.* v. *United States Plywood*

Corp., 258 F.2d 124, 136, 118 USPQ 122, 132 [*8] (2d Cir.) *cert. denied,* 358 U.S. 884 * * * (1958). *Shatterproof Glass,* 758 F.2d at 624, 225 U.S.P.Q. at 641.

The amendments to the claims reasonably apprise those skilled in the art of both the utilization and scope of the invention, and the language is as precise as the subject matter permits. Therefore the claims are supported in the specification as filed, and the claims are commensurate with the scope of the specification.

4. Rejection of claims 1, 18, 20-24, 26, 27, 29-34, 36-39, and 41-48 under 35.U.S.C. 112.

Claims 18, 24, 27, 32, 34, 39, 42, and 46-47 have been canceled by this Amendment. Reconsideration of the rejection of claims 1, 20-23, 26, 29-31, 33, 36-38, 41, 43-45, and 48 under 35.U.S.C. 112 first paragraph is respectfully requested for the following reasons. Claims 1, 26, 33, 38, and 45 (and hence their respective dependent claims) have been amended to recite that the antibody binds a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM (see, p. 8, lines 3-6; p. 1-, lines 22-23; and p. 11, lines 1-4). The claims also have been amended to recite the B cell subpopulations disclosed in the specification (see. e.g., Table 2). Therefore, the amended claims are within the scope of the specification as filed (therefore, the claims do not constitute new matter).

5. Rejection of claims 1, 18, 20-24, 26, 27, 29-34, 36-39, and 41-48 under 35.U.S.C. 112.

Claims 18, 24, 27, 32, 34, 39, 42, and 46-47 have been canceled by this Amendment. Reconsideration of the rejection of claims 1, 20-23, 26, 29-31, 33, 36-38, 41, 43-45, and 48 under 35.U.S.C. 112 first paragraph is respectfully requested for the following reasons. Claims 1, 26, 33, 38, and 45 (and hence their respective dependent claims) have been amended to recite that the affinity ligand is a monoclonal antibody which is a human antibody, murine antibody, or has both human antibody region and murine antibody region. The language in the claims is specifically taught in the specification as

filed (see, beginning last line on page 11, through page 12, and onto lines 1-4 on page 13), and is reasonably conveys to the artisan that the inventor had possession at the time of the invention. A CD 19 antibody of murine origin, human origin, or chimera of murine antibody and human antibody, was known in the art at the time of the invention.

6. Rejection of claims 1, 18, 20-24, 26, 27, 29-34, 36-39, and 41-48 under 35.U.S.C. 112.

Claims 18, 24, 27, 32, 34, 39, 42, and 46-47 have been canceled by this Amendment. Reconsideration of the rejection of claims 1, 20-23, 26, 29-31, 33, 36-38, 41, 43-45, and 48 under 35.U.S.C. 112 second paragraph is respectfully requested for the following reasons. Claims 1, 26, 33, 38, and 45 (and hence their respective dependent claims) have been amended to recite that the antibody binds a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM. Thus, the specification and the claims are commensurate in scope, and teach those skilled in the art how to make and use the claimed invention without undue experimentation (*Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q. 2d 1001, 1004 (Fed. Cir. 1997)).

7. Regarding the application of references the Examiner has cited as prior art, this is a continuation application entitled to the priority of the parent application for the reasons stated above in items 2-5 herein.

8. Rejection of claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 under 35.U.S.C. 102.

Claims 18, 24, 27, 34, 39, 42, and 46-47 have been canceled by this Amendment. Reconsideration of the rejection of claims 1, 20-23, 33, 36-38, 41, 43-45, and 48 under 35.U.S.C. 102(b) is respectfully requested for the following reasons. The U.S. Court of Appeals for the Federal Circuit court has repeatedly stated that anticipation under 35 U.S.C. 102 can only be established by a single prior art reference which discloses each and every element of the claimed invention. *RCA Corp. v. Applied Digital Data Systems,*

Inc., 730 F.2d 1440, 1444, 221 U.S.P.Q. (BNA) 385, 388 (Fed. Cir. 1984); *Radio Steel & Mfg. Co. v. MTD Products, Inc.*, 731 F.2d 840, 845, 221 U.S.P.Q. (BNA) 657, 661 (Fed. Cir. 1984); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 772, 218 U.S.P.Q. (BNA) 781, 789 (Fed. Cir. 1983); *SSIH Equipment, S.A. v. U.S. Int'l. Trade Comm'n.*, 718 F.2d 365, 377, 218 U.S.P.Q. (BNA) 678, 688 (Fed. Cir. 1983). In other words, the cited reference must identically disclose and describe the claimed invention for the reference to anticipate the claimed invention under 35 U.S.C. 102. What Meyer et al. teaches is that diagnostic antibodies or therapeutic antibodies used to treat humans can be recognized by the host's B lymphocytes which themselves may produce antibodies to neutralize the therapeutic antibody or diagnostic antibody (see p, 2, lines 7-20). Meyer et al. teach using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered therapeutic or diagnostic antibody (p.2, 38-40), not to treat a pro-MS immune response or MS itself. In this latest Office Action, the Examiner recognized that Meyer teaches use of anti-B cell antibody recognizing the Lym-1 determinant with other antibodies. The Examiner states that the claims under consideration in the present application are open in scope to encompass the administration of other antibodies in combination with the anti-Lym-1 antibody; and hence, is a proper §102 reference. The Applicants respond that the amendments to the claims have further defined the scope of the invention- "the composition consists of an affinity ligand consisting of a monoclonal antibody that is human, murine, or both human and murine, wherein the monoclonal antibody binds to a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM". Hence, the methods recited in the amended claims encompass only the administration of a single type of antibody, and not multiple antibodies as taught by Meyer et al. Therefore, Meyer et al. does not identically disclose and describe the claimed invention within the meaning of 35 U.S.C. 102.

Further, for the reasons stated by the Examiner in the previous Office Actions for the instant application, which the Examiner held "final" in the instant Office Action, a method depleting B cells with a B cell determinant of Lym-1 is patentably distinct from a method of depleting B cells with a B cell determinant of CD19. CD19 is a determinant not limited to expression on mature B cells, as is the antibody to Lym-1 using in the method described by Meyer et al. Rather, CD19 is expressed on most B cells (immature and mature; See also the Appendix A previously submitted by Applicants; "Principal Features of Known CD Molecules" from Cellular and Molecular Immunology). Thus, as the Examiner has stated in the previous Office Actions, the determinants are chemically and functionally distinct, and therefore patentably distinct. MPEP 706.02(b) states that a rejection based on 35 U.S.C. 102(b) can be overcome by establishing that the claims are patentably distinguishable over from the reference cited as prior art. In summary, Meyer et al. does not identically disclose or describe the method recited in amended claims 1, 20-23, 33, 36-38, 41, 43-45, and 48, and therefore, the claims cannot be anticipated by Meyer et al. under the meaning of 25 U.S.C. 102(b). Accordingly, it is respectfully requested that this rejection be withdrawn.

9. Rejection of claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 under 35.U.S.C. 103. Claims 18, 24, 27, 34, 39, 42, and 46-47 have been canceled by this Amendment. Reconsideration of the rejection of claims 1, 20-23, 33, 36-38, 41, 43-45, and 48 under 35.U.S.C. 103(a) is respectfully requested for the following reasons. In the instant Office Action, the Examiner rejects claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 under 35 U.S.C. 103 as being unpatentable over Meyer et al. in view of Pesando (WO 91/13974) and Arrufo et al. The remarks below are made with reference to the amended claims herein.

A. The Examiner is respectfully reminded that "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In*

re Wesslau, 353 F.2d at 241, 147 U.S.P.Q. at 393. In that regard, Meyer et al. do not teach treatment of progressive MS with anti-B cell antibody Lym-1. What Meyer et al. teaches is using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered therapeutic or diagnostic antibody (p.2, 38-40), not to treat a pro-MS immune response or MS itself. No disclosure of using the anti- B cell antibody Lym-1 to treat a pro-MS immune response and/or progressive MS is made. Rather, on page 3, lines 48-50, it is the therapeutic monoclonal antibody that is taught to be used in diseases such as progressive MS, not the anti- B cell antibody Lym-1. In response the Examiner states that the claims are open in scope and therefore encompass use of other antibodies in the composition. The Applicants respond that the amendments to the claims have further defined the scope of the invention- "the composition consists of an affinity ligand consisting of a monoclonal antibody that is human, murine, or both human and murine, wherein the monoclonal antibody binds to a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM". Hence, the methods recited in the amended claims encompass only the administration of a single type of antibody, and not multiple antibodies as taught by Meyer et al. Thus, the contribution of the Meyer et al. reference to the combination of references cited by the Examiner under §103 fails to make the amended claims obvious within the meaning of §103(a).

B. The Applicants appreciate the reminder by the Examiner under MPEP section 716.01(c). The Applicants respond that the evidence of record fails to make a prima facie case of obviousness for the following reasons.

a) Arrufo et al. teaches using a pan-immune cell antibody recognizing the determinant CD40 (expressed by B cells, dendritic cells, keratinocytes, monocytes, macrophages, epithelial cells, endothelial cells, fibroblasts, eosinophils, and T cells). It is well known at the time of the invention that T cells and macrophages play a major role in causing multiple sclerosis (see, e.g., the instant application at p. 2 lines 10-21, and Table 1). Thus, use of an antibody against CD40 affects T cells and macrophages, and which constitutes a treatment totally different in function and therapeutic effect than

depleting B cells associated with a pro-multiple sclerosis immune response. Pesando et al. teach a dual antibody approach, the combination of an antibody which binds to sIg on B cells and an antibody to CD19 in the form of a CD-19 specific immunoconjugate; and that only a subset of B cells possess sIg (see, for example, p. 4, lines 5-13). The combination of sIg and CD19 antibodies to form the immunoconjugate is directed to internalizing the immunoconjugate to the intracellular compartment of targeted B cells (see p. 3, lines 13-17). None of Meyer et al., Arrufo et al., or Pesando et al. individually, or combined could result in the treatment of (i) a pro-multiple sclerosis immune response (which was unknown until disclosed by the instant application); (ii) reducing a pro-multiple sclerosis immune response by using a composition which targets specific B cell subopulations involved in a pro-MS immune response cells using an antibody targeting a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM. To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of a claim against the prior art". *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494,496 (CCPA, 1970). See also, MPEP 2143.03. Due to the unobviousness of the elements of the claimed method according to the invention, the subject matter as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made.

b) A prior art reference must be considered in its entirety, i.e., as a whole, including the portions that would lead or teach away from the claimed invention. *United States v. Adams* 383 U.S.39, at 51-52 (Supreme Court 1966); *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 721 F. 2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983). See also MPEP 2145. Further, the references cannot be combined where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983). See also, MPEP 2145. Each of Meyer et al., Arrufo et al., and Pesando et al. teaches away from the claimed invention. Meyers et al. teaches using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic

antibody to suppress an immune response against the administered therapeutic or diagnostic antibody, not to treat a pro-MS immune response or MS itself. Arrufo et al. teaches using a pan-immune cell antibody recognizing the determinant CD40, not a determinant expressed by B cells and not by other immune cells. Pesando et al. teach a dual antibody approach, the combination of an antibody which binds to sIg on B cells and an antibody to CD19 in the form of a CD-19 specific immunoconjugate; and that only a subset of B cells possess sIg. These references, either singly or combined, teach away from using an antibody recognizing a determinant on B cells, such as CD19, to deplete B cells for reducing a pro-multiple sclerosis immune response. Instead they teach using combinations of antibodies, and/or antibody recognizing many different cell types other than B cells. Further, when combining the teachings and suggestions of Meyers et al., Arrufo et al. and Pesando et al., and taking their scope and content as a whole, one of ordinary skill in the art would still fail to come up with the claimed invention (let alone a reasonable expectation of success to make the claimed invention).

c) The Examiner responds that "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, the technique is obvious unless the actual application is beyond his or her skill". First, the present claims are not directed to a technique for improving a device. Secondly, the Examiner uses the operative word "would". The Applicants assert that (a) the initial burden of establishing a prima facie case of obviousness has not been met; and (b) that the invention recited in amended claims was not obvious to one of ordinary skill in the art at the time of the invention by the combination of the Meyers et al., Arrufo et al, and Pesando et al references.

The Examiner is respectfully reminded that in determining whether or not a claimed invention is obvious, it is important to evaluate what the skilled person in the art at the time of the invention would have done, **not** what that person could have done. The statutory standard requires us to decide whether the subject matter of the claimed invention "would have been obvious at the time the invention was made to a person of ordinary skill in the art to which [the subject matter of the invention] pertains." 35 U.S.C.

§ 103(a); Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006); DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006) (emphasis added). It is the initial burden of the Examiner to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to carry out the claimed process. The examiner bears the initial burden of establishing prima facie obviousness. See Ex parte Martin Gleave and Hideaki Miyake (84 U.S.P.Q.2D 1681 (Board of Patent Appeals and Interferences, 2006)) citing In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (emphasis added). The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.,* 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986). In determining this skill level, the court may consider various factors including "type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *Id. (cited in In re GPAC,* 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995)).

A "patent's subject matter can be proved obvious [is] by noting that there existed a known problem for which there was an obvious solution encompassed by the patent claims" *KSR*, 127 S. Ct. at 1742, 82 USPQ2d at 1397. As the Court in *KSR* states, required is consideration of common knowledge and common sense, at the time of the invention, to avoid hindsight reconstruction in assessing obviousness. "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention" *Innogenetics v. Abbott Laboratories*, 512 F.3d 1363; 85 U.S.P.Q. 2D 1641 (Fed. Cir. 2008).

The claimed invention relates to methods of for reducing a pro-multiple sclerosis immune response (as further defined in the claims) by administering to a human

individual an affinity ligand consisting of a monoclonal antibody that is human, murine, or both human and murine, wherein the monoclonal antibody selectively binds to a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM on a subpopulation of B cells selected from the group consisting of mature B cells, memory B cells, $CD19^{+}sTn^{+}$ B cells, $CD19^{+}CD21^{+}sTn^{+}$ B cells, and $CD19^{+}CD5^{+}sTn^{+}$ B cells, or a combination, to deplete said B cells. One of ordinary skill in the art, at the time of the invention would **not** have had the common knowledge and common sense to combine the references cited by the Examiner to carry out the claimed process, nor do the combination of references result in the claimed process. It was unknown to those skilled in the art at the time of the invention that shed antigen, having a 2,6 linked sialic acid component and produced during CNS tissue damage resulting from the inflammatory process of MS, activates a humoral immune response that exacerbates MS ("a pro-MS immune response"). This pro-MS immune response involves certain B cell subpopulations, also recited in the amended claims as the target of the method of the claimed invention. Without hindsight reconstruction (i.e., one of skill in the art could have looked at these references to devise a solution to a problem that was not known to them at the time of the invention), at the time of the invention one of skill in the art with common knowledge and common sense would not have looked to the references cited by the Examiner to come up with a method of the claimed invention, absent a reason for (i.e., knowing the problem solved by the method of the claimed invention) looking to those references in an attempt to come up with the method of the claimed invention. The Court in *KSR* also acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination (*KSR,* 127 S. Ct. at 1731). Thus, what the claimed invention provides, and what is not apparent to one of skill in the art at the time of the invention with common knowledge and common sense, is the development of a method for treating a pro-MS immune response involving a shed antigen having a 2,6 linked sialic acid eptope which activates a humoral immune response, as demonstrated by novel B

cell subpopulations found in the MS patients with a pro-MS response, that exacerbates the MS disease process. There is simply no appreciation, prior to the work of the present inventors, that such a pro-MS response existed, let alone a need for treating it.

The Examiner is also reminded that an invention would not be deemed obvious if all that was suggested "was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1166-67 (Fed. Cir. 2006).

In view of the foregoing, the invention recited in claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 is patentable over the combination of Meyer et al. in view of Pesando (WO 91/13974) and Arrufo et al. within the meaning of under 35 U.S.C. 103. Accordingly, it is respectfully requested that this rejection be withdrawn.

10. In the instant Office Action, the Examiner rejects claims 20, 26, 27, 29-32 under 35 U.S.C. 103 as being unpatentable over Meyer et al. in view of Pesando (WO 91/13974), Arrufo et al., and Turk et al. (U.S. Patent No. 5,958,409). Claim 27 has been canceled by this Amendment. Reconsideration of the rejection of claims 20, 26, 29-32, under 35.U.S.C. 103(a) is respectfully requested in view of the amendments to the claims, and for the reasons stated (including case law citations, MPEP sections, and evidence of nonobviousness) as applied to the reconsideration of the rejection under section 103 of claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 in view of the combination of Meyer et al. in view of Pesando (WO 91/13974) and Arrufo et al.

The contribution of Turk et al. to the cited combination is that Turk et al. disclose a method for treating multiple sclerosis using an anti-TNF-antibody. As explained in Turk et al. (column 3, lines 12 to 21), TNF is a secreted (not determinant found on) *in vivo* by monocytes and macrophages, and possibly some T cell subpopulations; and Turk et al.

describe CNS-directed antibody administration using an anti-TNF-antibody. The combination of references fail to make the claimed invention obvious for the reasons which can be summarized as follows.

a) None of Meyer et al., Arrufo et al., Pesando et al., or Turk et al. individually, or combined would result in (i) a treatment of a pro-multiple sclerosis immune response (which was unknown until disclosed by the instant application as described in more detail above in point 9 herein); (ii) methods of for reducing a pro-multiple sclerosis immune response (as further defined in the claims) by administering to a human individual an affinity ligand consisting of a monoclonal antibody that is human, murine, or both human and murine, wherein the monoclonal antibody selectively binds to a determinant selected from the group consisting of CD19, CD20, CD21, CD22, Lym-1, and CDIM on a subpopulation of B cells selected from the group consisting of mature B cells, memory B cells, $CD19^{+}sTn^{+}$ B cells, $CD19^{+}CD21^{+}sTn^{+}$ B cells, and $CD19^{+}CD5^{+}sTn^{+}$ B cells, or a combination, to deplete said B cells.

b) One of ordinary skill in the art, at the time of the invention would **not** have had the common knowledge and common sense to combine the references cited by the Examiner to carry out the claimed process, nor do the combination of references result in the claimed process. It was unknown to those skilled in the art at the time of the invention that shed antigen, having a 2,6 linked sialic acid component and produced during CNS tissue damage resulting from the inflammatory process of MS, activates a humoral immune response that exacerbates MS ("a pro-MS immune response"). This pro-MS immune response involves certain B cell subpopulations, also recited in the amended claims as the target of the method of the claimed invention. One of ordinary skill in the art would not combine the references at the time of the invention if that person, at the time of the invention, lacks the reason to combine the references. The Court in *KSR* also acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination (*KSR,* 127 S.

Ct. at 1731). Thus, what the claimed invention provides, and what is not apparent to one of skill in the art at the time of the invention with common knowledge and common sense, is the development of a method for treating a pro-MS immune response involving a shed antigen having a 2,6 linked sialic acid epitope which activates a humoral immune response, as demonstrated by novel B cell subpopulations found in the MS patients with a pro-MS response, that exacerbates the MS disease process. There is simply no appreciation, prior to the work of the present inventors, that such a pro-MS response existed, let alone a need for treating it.

c) A prior art reference must be considered in its entirety, i.e., as a whole, including the portions that would lead or teach away from the claimed invention. Further, the references cannot be combined where the references teach away from their combination. Each of Meyer et al., Arrufo et al., Pesando et al., and Turk et al. teaches away from the claimed invention. Meyers et al. using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered therapeutic or diagnostic antibody, not to treat a pro-MS immune response or MS itself (note the claims have been amended to recite that the antibody administered consists of an antibody-; i.e., the claims are not open ended to administration of multiple antibodies). Arrufo et al. teaches using a pan-immune cell antibody recognizing the determinant CD40, not a determinant expressed by B cells and not other immune cells. Pesando et al. teach a dual antibody approach, the combination of an antibody which binds to sIg on B cells and an antibody to CD19 in the form of a CD-19 specific immunoconjugate; and that only a subset of B cells possess sIg. Turk et al. teaches away from using an antibody recognizing (i) B cells, and (ii) a cell surface determinant (as Turk et al. teaches, TNF is a secreted molecule). These references, singly or combined, teach away from using an antibody recognizing a determinant on B cells, such as CD19, to deplete B cells for reducing a pro-multiple sclerosis immune response. Instead they teach using combinations of antibodies, and/or antibody recognizing many different cell types other than B cells, or

soluble, secreted molecules rather than cell determinants. Further, when combining the teachings and suggestions of Meyers et al., Arrufo et al., Pesando et al., and Turk et al., and taking their scope and content as a whole, one of ordinary skill in the art would still fail to come up with the claimed invention (let alone a reasonable expectation of success to make the claimed invention).

In view of the foregoing, the invention recited in claims 20, 26 and 29-32 is patentable over the combination of Meyer et al. in view of Pesando (WO 91/13974), Arrufo et al., and Turk et al. within the meaning of under 35 U.S.C. 103. Accordingly, it is respectfully requested that this rejection be withdrawn.

In view of the claim amendments, and the remarks including the citation of supporting case law and MPEP sections, Applicants believe the claims now meet the requirements of patentability under 35 USC §§ 112, 102, and 103.

Respectfully submitted,

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